Effect of the Inflammation, Chronic Hyperglycemia, or Malabsorption on the Apolipoprotein A-IV Concentration in Type 1 Diabetes Mellitus and in Diabetes Secondary to Chronic Pancreatitis

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The metabolism of apolipoprotein (apo) A-IV in diabetes mellitus (DM) is poorly understood. Several factors, such as dietary fat intake, fat malabsorption, acute inflammation, and hormonal dysregulation can disturb the plasma apo A-IV concentration. We have compared the plasma apo A-IV concentrations in patients with type 1 DM and DM secondary to chronic pancreatitis to determine the effects of combinations of these factors. We examined 4 groups of male patients with chronic pancreatitis without diabetes (ND-CP) (n = 12), diabetes secondary to chronic pancreatitis and insulin-treated (CP-DM) (n = 32), type 1 diabetes (n = 25), and controls (n = 20). Plasma apo A-IV was significantly lower in the chronic pancreatitis patients (ND-CP and CP-DM) than in the other patients. Inflammatory proteins (fibrinogen, ceruloplasmin, and haptoglobin) were significantly elevated in the 2 chronic pancreatitis groups. The apo A-IV concentration was positively correlated with hemoglobin A_{1c} (HbA_{1c}) percentage in each group of diabetic patients (CP-DM, $r = .35$; $P = .046$; type 1 DM, $r = .53$; $P = .010$), in both groups of diabetic patients ($r = .472$; $P < .0001$) and negatively correlated with ceruloplasmin concentration in each group of diabetic patients (CP-DM, $r = -.48$; $P = .0052$; type 1 DM, $r = -.66$; $P = .003$), in both groups of diabetic patients ($r = -.561$; $P < .0001$), and in the whole population ($r = -.463$; $P < .0001$). Apo A-IV was also negatively correlated with haptoglobin in type 1 DM patients ($r = -.434$; $P = .0435$), in the both groups of diabetic patients ($r = -.349$; $P = .0154$), and in the whole population ($r = -.351$; $P = .0019$). Multiple linear regression analysis revealed that only HbA_{1c} and ceruloplasmin were independent explanatory variables. Plasma apo A-IV is positively correlated with HbA_{1c} suggesting that hyperglycemia per se selectively affects apo A-IV metabolism. The correlation between the concentrations of inflammatory protein and apo A-IV suggest a link between chronic inflammation and apo A-IV synthesis or catabolism. As apo A-IV is involved in reverse cholesterol transport, its low level in CP-DM may contribute to the accelerated development of atherosclerosis in these patients.

ATHEROSCLEROTIC COMPLICATIONS are the major causes of death in type 1 diabetes mellitus (DM) patients. Quantitative and qualitative abnormalities of lipoproteins are present in type 2 DM and in poorly controlled type 1 DM, whereas patients who are well and moderately well-controlled have only qualitative abnormalities of their lipoproteins.[1,2]

The metabolism of plasma lipoproteins in these patients may be altered in a way that increases the atherogenicity of apolipoprotein (apo) B-containing lipoprotein (ie, increased low-density lipoprotein [LDL] oxidation) and/or to decrease the antiatherogenic effect of high-density lipoprotein (HDL) by altering reverse cholesterol transport. Lipoprotein metabolism depends on the apo content of lipoproteins. Apo A-IV is one of the minor apolipoproteins in triglyceride-rich apo B-containing lipoproteins (chylomicron, very–low-density lipoproteins [VLDL]) and in apo A-I-containing lipoproteins (HDL).

The metabolism of apo A-IV in type 1 DM is poorly understood. Apo A-IV acts as a link between the precursor of the atherogenic lipoproteins (ie, intermediate density lipoproteins [IDL] and LDL), such as the triglyceride-rich apo B-containing lipoproteins (VLDL) and the antiatherogenic apolipoprotein A-I containing lipoproteins (HDL). Apo A-IV activates lecithin cholesterol acyl-transferase (LCAT),[3] which is involved in the efflux of free cholesterol from the cell (the early step in reverse cholesterol transport). Apo A-IV itself also increases by the efflux of cholesterol from the cell.[4,5] Apo A-IV modulates the activity of proteins involved in the remodeling and clearance of atherogenic triglyceride-rich lipoprotein and in HDL metabolism[6-8] (cholesteryl ester transfer protein [CETP], lipoprotein lipase [LPL]). But the catabolism of HDL-cholesterol ester is accelerated in apo A-IV-deficient mice,[9] suggesting that a high concentration of apo A-IV increases the concentration of HDL-cholesterol by inhibiting the breakdown of HDL-cholesterol ester.

However, the physiologic and environmental factors that control the plasma concentration of apo A-IV are not clearly defined. Several factors can disturb the plasma apo A-IV concentration, such as dietary fat intake and fat malabsorption,[10,11] abnormal metabolism (hypertriglyceridemia and hyperglycemia[12], hormonal dysregulation,[13] and acute inflammation.[14,15] However, the relationship between apoA-IV and inflammation has never been described in humans to the best of our knowledge. Inflammation is considered to be a major feature of atherosclerosis, and some inflammatory glycoproteins are risk markers for atherosclerosis and cardiovascular disease.[16-18] Elevated concentrations of acute phase proteins, such as ceruloplasmin, may also signal abnormally high-oxidant stress.[19] We have attempted to discriminate between the effects of the diabetic state per and the type of diabetes by studying patients with diabetes secondary to chronic pancreatitis. Atherogenesis

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is accelerated in these patients, as it is in patients with type 1 diabetes, even though they have even lower plasma LDL cholesterol concentrations.[20-22] Lipid malabsorption due to chronic pancreatitis is also known to decrease the apo A-IV concentration,[10,11] so there could be a wide range of apo A-IV concentrations in patients with chronic pancreatitis. However, the effect of chronic hyperglycemia on the concentration of apo A-IV has never been determined in patients with diabetes secondary to chronic pancreatitis. DM secondary to chronic pancreatitis could be a useful model in which to study the combined effects of different factors altering plasma apo A-IV levels, such as chronic hyperglycemia, lipid malabsorption, and inflammation.

We have therefore compared the plasma apo A-IV concentrations of type 1 diabetic patients with those of patients suffering from DM secondary to chronic pancreatitis, patients with chronic pancreatitis, but without diabetes, and controls. We have also assessed the interactions between the degree of plasma glucose control, inflammatory markers, and fat malabsorption on plasma apo A-IV.

MATERIALS AND METHODS

Subjects

We examined 4 groups of men. These were subjects with chronic pancreatitis without diabetes (ND-CP) (n = 12), diabetes secondary to chronic pancreatic and insulin-treated (CP-DM) (n = 32), type 1 diabetes (n = 25), and controls (n = 20). The patients with type 1 DM were individually matched for age and diabetes duration (± 2 years) with the CP-DM patients. The control subjects were matched for social category and age with the ND-CP patients (Table 1).

Chronic pancreatitis was diagnosed on the basis of clinical history and the presence of morphological pancreatic abnormalities, especially calcification detected by x-ray and confirmed by abdominal ultrasonography, computerized tomography, or echoendoscopy. All CP-DM and 10 of 12 ND-CP patients had calcific pancreatitis. One patient was diagnosed by ultrasonography scanner and another by echoendoscopy.

All the patients in the CP-DM group had stopped or greatly reduced their alcohol intake by the time of the study (Table 1). They had consumed less than 30 g/d for 5 years. Their former alcohol consumption was 111 ± 66 g/d (range, 50 to 450 g/d) for a period of 25.5 ± 11.4 years. They had undergone 3 choledoco-jejunostomies and 4 cystic derivations. Patients with pancreatectomy or gastrectomy were excluded. All patients in group CP-DM had diabetes according to the criteria of the American Diabetes Association[23] and had been on insulin for at least 3 months. No patient had suffered from acute pancreatitis for the past 3 months. All the patients in group ND-CP had normal fasting plasma glucose on the day they entered the study (fasting plasma glucose < 6.1 mmol/L) (Table 1).

Patients treated with pancreatic enzymes underwent a 5-day washout period. A 72-hour stool sample was collected from chronic pancreatitis patients on a home-made diet. Blood samples were collected after an overnight fast, before insulin injection, and then on the sixth day of the wash out period.

This study was approved by the ethical committee for the Protection of Human Subjects of Nancy (France).

Analytical Methods

The plasma glucose concentrations were measured by the glucose oxidase method using an automated glucose analyzer. Hemoglobin A_{1c} (HbA_{1c}) was determined as a percentage of the total hemoglobin following high-performance liquid chromatography (Diamat; BioRad Laboratories, Hercules, CA) (normal range, 4.5% to 6%). The fecal fat of the patients in the ND-CP group was analyzed according to Van de Kamer et al.[24] Albumin (normal range, 37.8 to 46.2 g/L), transferrin (normal range, 1.84 to 2.94 g/L), ceruloplasmin (normal range, 0.25 to 0.45 g/L), and haptoglobin (normal range, 0.6 to 1.6 g/L) were analyzed by nephelemetry using a ARRAY 360 system (Beckman, Brea, CA). Ferritin (normal range, 100 to 300 ng/L) and fibrinogen (normal range, 1.5 to 4.5 g/L) were analyzed on a Behring nephelemeter analyser-II (Marburg, Germany). HDL-cholesterol was obtained after precipitation of apo B-containing lipoproteins with sodium phosphotungstate/magnesium chloride (Boehringer, Mannheim, Germany). Total cholesterol and triglycerides were determined using commercial kits (Boehringer) adapted to a Hitachi 911 analyzer (Japan). LDL-cholesterol was calculated according to Friedewald et al.[25] Apo A-IV[26] was assayed by a noncompetitive enzyme-linked immunosorbent assay (ELISA), as were

Table 1. Subjects Characteristics

	ND-CP (n = 12)	CP-DM (n = 32)	Type 1 DM (n = 25)	Controls (n = 20)	ANOVA *P* Value
Age (yr)	48 ± 13[a]	57 ± 9[b]	55 ± 10[b]	44 ± 11	.0001
Diabetes duration (yr)	-	14 ± 7	17 ± 9	-	NS
Pancreatitis duration (yr)	4.8 ± 5.2	16.3 ± 7.7	-	-	.0001
Steatorrhea (g/d)	5.5 ± 5.2	12.0 ± 8.4	-	-	.0285
Fasting plasma glucose (mg/dL)	90 ± 10[a,c]	190 ± 70[d,e]	240 ± 90[e]	90 ± 20	.0001
HbA_{1c} (%)	-	8.6 ± 1.9	7.8 ± 1.0	-	NS
BMI (kg/m^2)	21 ± 3[a,b]	22 ± 3[b]	26 ± 4	25 ± 2	.0001
Alcohol (g/d)	3.8 ± 8.8[a,b]	7.2 ± 10.4[b]	13.3 ± 15.2	15.9 ± 16.9	.0282
Fat (g/d)	98 ± 30	99 ± 32	105 ± 30	124 ± 34	NS
CHO (g/d)	295 ± 74	290 ± 76	272 ± 58[b]	331 ± 95	NS
Protein (g/d)	112 ± 32	111 ± 29	111 ± 17	117 ± 25	NS
Energy (kJ/d)	10,044 ± 2,350[c]	10,046 ± 2,358[c]	10,321 ± 2,077[b]	12,496 ± 2,628	.0113

NOTE. Values are means ± SD.

Abbreviations: ND-CP, chronic pancreatitis without DM, CP-DM, chronic pancreatitis with insulin-treated DM, BMI, body mass index; CHO, carbohydrate; PL, phospholipides; LDL-Chol, low-density lipoprotein-cholesterol; HDL-chol, high-density lipoprotein-cholesterol; Apo, apolipoprotein; NS, not significant.

v CP-DM: [a]$P < .05$; [b]$P < .01$.

v type 1 DM: [c]$P < .05$; [d]$P < .01$; [e]$P < .001$.

v controls: [f]$P < .05$; [g]$P < .01$; [h]$P < .001$.

apo A-I,[27] apo A-II,[28] apo C-III,[29] and apo E.[30] Apo B was measured by immunonephelemetry (Behring, Marburg, Germany).

Data Analysis

Conventional methods were used to calculate means ± SD. Statistical analyses were performed with BMDP software (Berkeley, CA). Coefficients of skewness and kurtosis were calculated to test deviations from a normal distribution. Continuous variables were tested by 1-way analysis of variance (ANOVA) between the 4 groups. Comparisons among groups were performed using ANOVA. Student-Newman-Keuls comparison test was applied when ANOVAs were significant. Pearson's correlation was used for 2-variable relationships. Multiple regression analysis was used to assess the effects of several independent variables on apo A-IV. In the multiple regression analysis, we have taken account of the effects of DM (diabetics *v* without DM) and of chronic pancreatitis (with chronic pancreatitis *v* without chronic pancreatitis). $P < .05$ was considered significant.

RESULTS

The mean values of lipid parameters are shown in Table 2. The patients in both chronic pancreatitis groups (ND-CP and (CP-DM) had lower LDL-cholesterol and apo B concentrations than the controls and type 1 DM patients. Plasma Apo A-IV concentrations were significantly decreased in both groups of chronic pancreatitis patients (ND-CP and CP-DM), whereas there was no significant difference in these concentrations between the patients with type 1 DM and the control subjects. There were no significant differences in the plasma HDL-cholesterol, triglycerides, apo A-I, apo A-II, apo E, and apo C-III of the 4 groups.

Plasma ceruloplamin was significantly elevated in the CP-DM patients, while plasma fibrinogen and haptoglobin were significantly elevated in both the CP-DM and ND-CP groups (Table 3), whereas there were no significant differences in the concentrations of tranferrin, ferritin, and albumin of the 4 groups. The concentrations of inflammatory markers in the smokers and nonsmokers were similar (data not shown). Age was different between the 4 groups, however, we did not find any significant effect of age on these parameters.

We found a relationship between plasma apo A-IV and steatorrhea for all the chronic pancreatitis patients, but it was not significant ($r = .362$; $P = .082$).

The apo A-IV concentration was negatively correlated with ceruloplasmin in the chronic pancreatitis patients (ND-CP and CP-DM), independently of their DM status ($r = -.236$; $P = .008$), but not with lipid parameters, fasting plasma glucose, age, or body mass index (BMI).

The apo A-IV concentration was positively correlated with HbA_{1c} percentage within each group of diabetic patients (CP-DM, $r = .35$; $P = .046$; type 1 DM, $r = .53$; $P = .010$) and in the 2 groups of diabetic patients combined ($r = .472$; $P < .0001$) and negatively correlated with ceruloplasmin concentration in each group of diabetic patients (CP-DM, $r = -.48$; $P = .0052$; type 1 DM, $r = -.66$; $P = .003$), in the 2 groups of diabetic patients combined ($r = -.561$; $P < .0001$), and in the whole population ($r = -.463$; $P < .0001$). Apo A-IV was also negatively correlated with haptoglobin in type 1 DM patients ($r = -.434$; $P = .0435$), not significant (NS) in the CP-DM group ($r = -.207$, NS), but also significantly in the 2 groups of diabetic patients combined ($r = -.349$; $P = .0154$) and in the whole population ($r = -.351$; $P = .0019$). There was no correlation between the apo A-IV concentration and other lipid parameters, fasting plasma glucose, age, or BMI. Simple regression analysis on all the subjects showed that ceruloplasmin was highly correlated with haptoglobin ($P < .0001$) and fibrinogen ($P = .0031$).

The data from diabetic patients (type 1 DM and CP-DM) were analyzed by multiple linear regression (Table 4) to examine the contribution of HbA_{1c}, ceruloplasmin concentration, lipid parameters, and chronic pancreatitis to changes in apo A-IV concentration. Only HbA_{1c} and ceruloplasmin were independent explanatory variables.

DISCUSSION

Our main finding is that the plasma apo A-IV concentration positively correlated with HbA_{1c} and negatively with chronic

Table 2. Lipid Parameters

	ND-CP (n = 12)	CP-DM (n = 32)	Type 1 DM (n = 25)	Controls (n = 20)	ANOVA *P* Value
TC	192 ± 35[a]	157 ± 30[b,c]	194 ± 28	214 ± 23	<.0001
TG	136 ± 43	107 ± 51	101 ± 39	115 ± 43	NS
LDL-Chol	115 ± 25[d,e]	94 ± 23[b,c]	131 ± 24	144 ± 23	<.0001
HDL-Chol	51 ± 16	40 ± 13	46 ± 11	41 ± 17	NS
Apo A-IV	20.3 ± 7.3[c,f]	27.1 ± 13.9[g]	30.8 ± 15.3	36.7 ± 13.4	.009
Apo B	103 ± 19[d,g]	85 ± 25[c,h]	107 ± 26	120 ± 19	<.0001
Apo C-III	42 ± 25	36 ± 15	38 ± 19	32 ± 17	NS
Apo E	54 ± 30	43 ± 43	42 ± 33	39 ± 18	NS
Apo A-I	167 ± 39	146 ± 31	160 ± 21	156 ± 28	NS
Apo A-II	38 ± 1	35 ± 09	37 ± 011	38 ± 15	NS

NOTE. Values are means ± SD and expressed as mg/dL.

Abbreviations: ND-CP, chronic pancreatitis without DM, CP-DM, chronic pancreatitis with insulin-treated DM; TC, total cholesterol; TG, triglycerides; PL, phospholipides; LDL-Chol, low-density lipoprotein-cholesterol; HDL-chol, high-density lipoprotein-cholesterol; Apo, apolipoprotein; NS, not significant.

v CP-DM: [a]$P < .05$; [b]$P < .01$.

v type 1 DM: [c]$P < .05$; [d]$P < .01$; [e]$P < .001$.

v controls: [f]$P < .05$; [g]$P < .01$; [h]$P < .001$.

Table 3. Inflammatory Proteins

	ND-CP (n = 12)	CP-DM (n = 32)	type 1 DM (n = 25)	Controls (n = 20)	ANOVA *P* Values
Ceruloplasmin (g/L)	0.36 ± 0.09	0.38 ± 0.07[a]	0.34 ± 0.07	0.31 ± 0.08	0.0314
Haptoglobin (g/L)	1.83 ± 0.82[a,b]	1.38 ± 0.83[c]	1.23 ± 0.57	1.11 ± 0.41	0.0451
Fibrinogen (g/L)	3.49 ± 0.56[c]	3.44 ± 1.11[c]	3.01 ± 0.53	2.75 ± 0.54	0.0242

NOTE. Values are means ± SD.

Abbreviations: ND-CP, chronic pancreatitis without DM, CP-DM, chronic pancreatitis with insulin-treated DM.

v type 1 DM: [c]$P < .05$.

v controls: [f]$P < .05$; [g]$P < .01$.

inflammation markers. The apo A-IV concentrations in both CP groups (CP-DM and ND-CP) were dramatically decreased, and apo A-IV was slightly, but not significantly, lower in type 1 DM than in controls because of the opposing influences of poor plasma glucose control and inflammation.

The precise function of apo A-IV, which is synthesized by the intestine in humans[31] in lipid metabolism remains unclear. Patients with chronic pancreatitis were included in this study to take into account the potential effects of dietary fat intake and absorption. Steatorrhea, a crude marker of exocrine pancreas insufficiency, was significantly elevated (>5 g/d) in 5 of 12 ND-CP patients and in 26 of 32 CP-DM patients. There was a trend towards a correlation between steatorrhea and plasma apo A-IV concentration. The postprandial apo B-48 concentration, which is a more sensitive marker of fat malabsorption,[32] was significantly and positively correlated with the apo A-IV concentration in a subgroup of the CP patients ($r = .42$; $P < .01$; n = 32, data not shown). Finally, the daily fat intakes of the CP-DM and type 1 DM subjects were lower than those of controls, which may have contributed to the surprisingly low plasma apo A-IV in these groups. The low apo A-IV concentration could reflect low apo A-IV synthesis by the intestine due to low fat absorption in the intestine.[31] Nevertheless, fat malabsorption or low fat intake might not be the only factors leading to a decrease in apo A-IV concentration.

It has been suggested that inflammation is an important determinant of plasma apolipoprotein concentrations, such as apo A-I,[33,34] apo E,[35] and apo A-II.[15] Inflammation can also increase the plasma concentrations of lipoprotein particles, such as LpB-CIII (lipoprotein particles containing apo B and apo C-III).[36] Tu et al[15] and Shen et al[14] have clearly demonstrated that acute inflammation decreases hepatic apo A-IV mRNA in rats. Nevertheless, we have found no published data on the effect of inflammation on apo A-IV synthesis by the intestine.

Table 4. Multiple Linear Regression Analysis: Influence of Selected Variable on Plasma apo A-IV Levels in Diabetic Patients (CP-DM and type 1 DM, n = 64)

Parameter	*r**	r^2	$P = .002$
HbA_{1c}	0.325	0.11	.0111
Ceruloplasmin	−0.537	0.29	<.0001
HDL-Chol	−0.016	-	NS
TG	0.003	-	NS
CP	−0.012	-	NS

*Partial correlation coefficient.

Abbreviation: CP, chronic pancreatitis.

We find that the plasma concentrations of some inflammatory proteins are higher in patients with chronic pancreatitis (both in ND-CP and CP-DM groups) than in controls. Hence, inflammation might help to reduce plasma apo A-IV in these patients. Acute-phase serum proteins can be increased in DM,[37] and 15 of 25 of our type 1 DM patients had increased plasma concentrations of at least one of these inflammatory markers, which could indicate a negative effect of inflammation on apo A-IV concentration. We also find that plasma apo A-IV is closely, but negatively, correlated with the plasma concentration of 2 acute serum proteins (ceruloplasmin and haptoglobin). Thus, inflammation could be one of the factors regulating plasma apo A-IV in DM. Perhaps changes in the apo A-IV concentration due to chronic inflammation influence cardiovascular risk in diabetic patients.

There is convincing evidence that chronic mild inflammation is involved in the progression of atherosclerosis.[38] The increase in plasma concentrations of acute-phase proteins, such as fibrinogen, C-reactive protein (CRP), glycoproteins, such as ceruloplasmin, the sialoglycoproteins (haptoglobin), and ferritin is associated with an increased risk of cardiovascular disease.[39-42] Several inflammatory proteins are also implicated in oxidant stress. The results of the Rotterdam study[42] suggest that serum ceruloplasmin is still a high-risk factor of myocardial infaction after adjustment for CRP and white cell count, probably because ceruloplasmin is not merely an indicator of inflammation, but also signals abnormally high-oxidant stress. This protein inhibits superoxide-induced lipid peroxidation,[43] which is greater in diabetics than in nondiabetics.[44,45] In contrast, apo A-IV inhibits LDL oxidation in vitro,[46] which is considered to cause the formation of foam cells and atherogenesis.[47,48] Consequently, apo A-IV and these inflammatory proteins are implicated in oxidative stress. Human apo A-IV transgenesis inhibits atherogenesis in hypercholesterolemic apo E-deficient mice independently of the HDL concentrations.[49,50]

Little is known about the role of blood glucose control on apo A-IV metabolism in diabetic patients, especially in type 1 DM. We find a positive correlation between plasma HbA_{1c} and apo A-IV in patients with diabetes secondary to chronic pancreatitis (CP-DM), as well as in type 1 diabetic patients, suggesting that the plasma apo A-IV concentration depends on plasma glucose control per se, independently of other factors.

The binding of Apo A-IV to lipoproteins is very labile, especially HDL[8,26] and could be very sensitive to glycation. However, Rader et al[51] showed that the fractional catabolic rate of apo A-IV is about 2.3/d, which is a residence time in the blood that is too short to permit its glycation.[45] The decrease of

apo A-IV in type 1 diabetics could be due to an increase in fractional catabolic rate due to others factors than apoprotein glycation. A few studies have attempted to measure the apo A-IV concentration in DM. Verges et al[12] showed that the apo A-IV concentration is increased in type 2 DM and is mainly linked to hypertriglyceridemia. A recent study[52] reported that plasma apo A-IV concentrations are increased in young people (7 to 19 years) with type 1 diabetes and that it is closely linked to the plasma glucose concentration. However, it has been reported that the plasma concentrations of inflammatory markers (acute-phase protein) are elevated in adult diabetics,[37] but are normal or nearly normal in diabetic children and adolescents.[53,54]

It is also possible that lipoprotein abnormalities are involved in the changes in apo A-IV concentration induced by DM. We find no significant correlation between the plasma apo A-IV concentration and lipid parameters such as plasma triglycerides, total cholesterol, or HDL cholesterol. Verges et al[12] demonstrated the opposite in type 2 diabetic patients treated with oral hypoglycemic agents. However, they found no significant relationship between apo A-IV and HDL-cholesterol or triglycerides in insulin-treated type 2 diabetics,[12] as our type 1 DM was normal. Perhaps insulin treatment might reduce apo A-IV synthesis in type 1 diabetics.[13]

Thus, our results suggest that hyperglycemia per se selectively affects apo A-IV metabolism. The correlation between the concentrations of inflammation protein and of apo A-IV suggests a relationship between chronic inflammation and apo A-IV synthesis or catabolism. This aspect of apo A-IV physiology is not clearly understood, but requires further investigation, because it could be involved in the pathogenesis of atherosclerosis in type 1 DM and in CP-DM.

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